Changes in the Options for Management of Prolactin Secreting Pituitary Adenomas

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Abstract

Objectives Initial therapy for the management of prolactinomas has long been maintained to be medical, consisting of a dopamine agonist. These therapies may have troublesome side effects, and some prolactinomas are resistant to medical therapy regarding lowering prolactin levels or shrinking the tumor. These issues have revived interest in surgery for prolactin-secreting adenomas as an early therapeutic option. We report our analysis of surgery for prolactin microadenomas in women, using the transsphenoidal endoscopic approach.

Design We reviewed a contemporary series of 33 women (mean age = 31.8 years) with microprolactinomas who underwent early surgical intervention, which was a three-dimensional transnasal transsphenoidal endoscopic operation.

Setting The study was conducted at a tertiary academic referral center for pituitary tumors.

Main Outcome Measures Preoperative and postoperative prolactin.

Results Overall, 28 patients had received preoperative dopamine agonists, 24 of these experienced a variety of drug-related side effects, and 4 had tumors that were resistant to lowering prolactin or tumor shrinkage. Preoperative prolactin levels averaged 90.3 ng/mL (range = 30.7–175.8 ng/mL). We observed a 94% normalization rate in postoperative prolactin (mean = 10.08 ng/mL, range = 0.3–63.1 ng/mL). During the follow-up (mean = 33.9 months), five patients had elevated prolactin; four required reinitiation of medical therapy, two had surgical reexploration, and none received radiation therapy. Complications included syndrome of inappropriate antidiuretic hormone secretion ($n = 3$), transient diabetes insipidus ($n = 1$), postoperative epistaxis ($n = 1$), and fat graft site infection ($n = 1$).

Conclusion This review supports the consideration of transsphenoidal surgery as an early intervention for some women with prolactin-secreting microadenoma. Indications include significant side effects of medical therapy and tumors that do not respond to standard medical management.

Keywords

- prolactinoma
- pituitary tumor
- dopamine agonist side effects
- endoscopic transsphenoidal surgery

Introduction

First characterized as the Forbes-Albright syndrome (amenorrhea-galactorrhea),[1] prolactin-secreting tumors are among the most common subtype of pituitary adenoma, occurring in 30 to 40% of most large series.[2] The identification and isolation of prolactin allowed for an accurate assay for serum prolactin to be developed in the 1970s. An early concern was that the tumors might be related to the initiation of contraceptive agents. This was investigated and disproven.[3] The tumors

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began to be recognized in some male patients as well as in women.

The development of accurate imaging, first with CT and then with MRI, allowed for the effective identification of these tumors and for calibration of their size, from microadenomas measuring less than 10 mm in diameter to macroadenomas which measured 10 mm or larger.[4] Although many of these tumors were well isolated, some were associated with cystic formation, and others with tumor cell invasion of the sellar and parasellar structures. Large prolactinomas with supra-sellar extension could present with visual loss, as well as hormonal dysfunction.

Surgical treatment rapidly evolved from craniotomy to microsurgical transsphenoidal approaches for the removal of pituitary tumors.[5–7] Initial surgical therapy by either method was usually effective, but often did not completely normalize prolactin levels, and initially postoperative recurrence was common.

A major therapeutic event was the development of neurotransmitter-based medical therapy, using dopamine agonists which were recognized as inhibiting the secretion of prolactin.[8–10] The initial form medical therapy was bromocriptine, which was given once or more daily, and was subsequently surpassed by cabergoline—a long-acting dopamine agonist which could be given twice a week, with great efficacy in lowering prolactin secretion and even in shrinking large tumors.[11,12] Once medical therapy was fully established, many consensus statements and guidelines for the therapy of patients with prolactinomas were developed.[13,14] In almost all of them, prior to the past year or two, medical therapy was essentially always recommended as the first-line therapeutic approach, and it has been the most utilized treatment modality for the management of prolactinomas of all sizes. Years of experience have helped endocrinologists in providing satisfactory therapy for most of their patients using these medical guidelines.[15] There has, however, been an increasing recognition of the relative frequency of serious side effects from dopamine agonists, particularly in women.[16–18] Additionally, there are some prolactin tumor variants that are resistant to the inhibiting effects of cabergoline and bromocriptine, thus requiring very high-drug doses, or not responding adequately at all.[19–21]

Surgical management has continued to be employed for selected patients, and it has become increasingly more commonly utilized over the past several years, particularly for smaller tumors (microadenomas). Surgical techniques, including minimally invasive endoscopic transnasal transsphenoidal surgery, have allowed the operations to be both safer and more precise, offering more complete and more permanent resections of the tumors.[22] Indications have expanded to consider surgical therapy to be most beneficial in patients who have tumors that are resistant to dopamine agonists in terms of lowering the serum prolactin levels, and also for patients who suffer from several serious medication-related side effects that impair their quality of life.

As these changes in management are becoming more commonly utilized, we sought to critically evaluate the current transnasal transsphenoidal microsurgical endoscopic approach for surgical removal of prolactinomas, particularly microadenomas in women. We planned to assess the efficacy of surgery in terms of removal of tumor tissue, restoration of prolactin elevation to normal, and the incidence of correction of side effects of medical therapy. Also, recorded were the complications and suboptimal effects that can occur with surgery.

Table 1 Characteristics of 33 patients in cohort

	Mean	Range
Age (y)	31.8	17–48
Preoperative prolactin (ng/uL)	92.3	30.7–175.8
Postoperative prolactin (ng/uL)	10.1	0.3–63.1
Length of follow-up (mo)	37.3	1–126

Patients and Methods

We performed a retrospective study of all patients operated upon by a single surgeon at a single institution for all pathologically proven prolactin adenomas, including microadenomas and macroadenomas, over the interval from April 2008 until February 2020. This study was approved by the institutional review board of the Brigham and Women's Hospital.

The study group consisted of a consecutive series of 33 prolactin microadenomas in women having initial surgery (no prior surgery). The transnasal transsphenoidal endoscopic operative procedure was performed in all patients. The age range was from 17 to 48 years with a mean age of 31.8 years (►**Table 1**). Ordinarily, when a patient agreed to have surgery, we ask them to discontinue dopamine agonist medication (bromocriptiine and cabergoline). We have found, however, that dopamine agonists taken for less than 3 years do not produce challenging changes in the nature of the prolactinoma.

Results

Cohort

Surgery was offered to 33 patients with prolactin-secreting microadenomas, primarily for the indications of intolerance to medication side effects ($n = 24$), lack of normalization of prolactin ($n = 4$), or personal preference ($n = 5$) (►**Table 2**). In the entire group of 33 women, preoperative dopamine agonist medications had been given to 28. Four patients had tumor resistance to lowering of prolactin, one had transient preoperative visual loss, and the remainder had a spectrum of physical and emotional side effects that are listed in ►**Table 2**.

The preoperative prolactin levels varied from 30.7 to 175.8 ng/mL, with a mean preoperative prolactin of 92.3 ng/mL. Postoperative prolactin levels, 1 to 6 weeks postoperatively, varied from 0.3 to 63.1 ng/mL, with a mean of 10.1 ng/mL. Normal prolactin range in our laboratory was 4.8 to 23.3 ng/mL. The initial normalization rate for hyperprolactinemia was 94%. Subsequent medical therapy was ultimately required in four patients.

Table 2 Side effects prompting surgery

Side effect	No. of patients
Headache	11
Nausea and vomiting	8
Dizziness	5
Cognitive difficulties	3
Depression	3
Fatigue	3
Anxiety	2
Insomnia	2
Presyncopal and hypotension	2
Drug interactions	2
Exacerbation of other psychological issues	2
Suicidal ideation	1
Inability to concentrate	1
Weight loss	1
Hypertension	1
Palpitations	1

Clinical Outcome

Among the five eventual recurrences of hyperprolactinemia, during a follow-up period of 1 to 126 months, mean 37.3 months, two of the five recurrent patients had subsequent repeat surgery none was given radiation therapy or radiosurgery, and the three others were managed medically. There were seven complications of surgery: syndrome of inappropriate antidiurectic hormone (SIADH) in three, transient diabetes insipidus (DI) in one, epistaxis in one, a fat graft wound complication in one, and postoperative sinusitis in one (►**Table 3**).

Histopathology Correlates

Histopathologic analysis confirmed immunopositivity for prolactin in all resected tumors, without excess expression of any other pituitary hormones. No tumors coexpressed prolactin and growth hormone in this cohort. The proliferation status was analyzed in 23 tumors on pathological testing by MIB-1 staining. The MIB-1 proliferation index ranged from less than 1 to 10%; 12 tumors had values less than 2%, nine tumors ranged from 2 to 3%, one between 5 and 9%, and one was at 10% (►**Table 4**).

Table 3 Complications of surgery

Complication	No. of patients
SIADH	3
Transient DI	1
Epistaxis	1
Fat graft site problem	1
Sinusitis	1

Abbreviations: DI, diabetes insipidus; SIADH, syndrome of inappropriate antidiurectic hormone.

Table 4 MIB-1 proliferation index across chort, for 23 patients with available values. MIB-1 values not available for 10 patients

MIB-1 proliferation index	No. of patients
<2%	12
2–3%	9
5–9%	1
10%	1

Discussion

Prolactinomas comprise a large proportion of pituitary tumors (~30–40%).[2] Fortunately, they are usually benign tumors. Metastatic spread and malignant behavior are uncommonly rare.

The discovery of the regulation of prolactin by way of the neurotransmitter dopamine is one of the most extraordinary examples of medical research leading to the regulation, not only of hormone secretion, but of the development and control of pituitary prolactin secreting adenomas. Dopamine agonists have been developed into safe and effective drugs (bromocriptine and cabergoline) that successfully treat the majority of prolactinomas, both by decreasing prolactin secretion and by shrinkage of the bulk of the associated tumor.[12] The effectiveness of dopamine agonists results in control of disease in 90% or more of patients.[11] An accurate and helpful series of consensus documents and guidelines for the treatment of prolactinomas has been published.[13,14] Although medical management has generally been recommended as initial therapy, experience has allowed for some situations—as mentioned above—in which other strategies may be considered.

With advances in neuroimaging and endocrine diagnosis, surgery had been increasingly applied as an effective means of removing prolactinomas.[23–32] Surgical resection was more readily accomplished in microadenomas and was also useful in macroadenomas, particularly those that did not respond to dopamine agonist therapy.[26,33]

In addition to the lack of tumor response in diminishing serum prolactin levels in refractory tumors, the drugs—as used in the usual fashion—were associated with several side effects.[16] Some of these were trivial problems, but others created major issues in quality of life. Alterations in drug dosage occasionally reversed these problems; however, there remains a proportion of patients in whom both short- and long-term treatment is presumably related to peripheral effects on the brain and other organs. Some patients with preexisting emotional, psychological, cognitive, and physical problems experienced exacerbation and amplification of symptoms while taking dopamine agonist therapy.[16–18] Unfortunately, there is little in the way of objective analysis of the proportion of prolactinoma patients who suffer the side effects of medical therapy. Early reports suggested that approximately 6% of patients with prolactinomas were

intolerant of dopamine agonist medication, both for symptomatic side effects and for ineffective reduction of prolactin levels in the blood.[33]

Intractable headache, usually similar to "migraine," is the most common symptom attributed by the patient to the dopamine agonist medication. This symptom is closely followed by nausea and vomiting, presyncopal feelings and hypotension, dizziness, and a significant number of psychological changes including anxiety, panic attacks, depression, inability to concentrate, and even suicidal thoughts. If surgery satisfactorily normalizes prolactin physiology, and medication is discontinued, more than two-thirds of these effects are ameliorated.[33]

Although some patients develop complete regression of the tumor with medical therapy, this usually requires many years of treatment before total involution of the tumor recurs and medication can be discontinued.[12] Some patients are reluctant to consider life-long medical management, and they comprise another group of patients for whom surgery may seem beneficial. These considerations collectively impact the choice of therapy.

Historically, studies of the surgical management of prolactinomas were promising, especially with the use of the microsurgical transsphenoidal approach.[23–32] Although effective initially, there was a relatively high postsurgical recurrence rate, approximating 12% within 10 years following surgery.[6] Recurrences can be treated with resumption of medical therapy, consideration of radiation therapy or radiosurgery, which have their own advantages and disadvantages, or possibly another surgical procedure.[29] It is evident that the results of surgery are optimal at high-volume centers with experienced pituitary surgeons.

Conclusion

The awareness of the possibility and relative frequency of disturbing side effects is probably the major driver for the growing number of reports of transsphenoidal endoscopic microsurgical removal of prolactinomas, primarily microadenomas. Most of the publications confirm a high degree of effectiveness and low rates of complications. Many patients plea for a reconsideration of surgery as a legitimate method of early intervention for select patients, particularly younger women, with significant side effects of dopamine agonist therapy. The current summary of our experience lends support to surgery as a viable patient-oriented strategy.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors. This study was approved by the institutional review board of the Brigham and Women's Hospital.

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None.

Conflict of Interest

None declared.

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